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**BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES**

Application Number: 10/518,727  
Filing Date: September 14, 2005  
Appellant(s): KRAUSE ET AL.

Frank C. Eisenschenk  
For Appellant

**EXAMINER'S ANSWER**

This is in response to the appeal brief filed 11/04/2010 appealing from the Office action mailed 07/08/2010.

**(1) Real Party in Interest**

A statement identifying the real party interest is contained in the brief.

**(2) Related Appeals and Interferences**

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

A statement that there are no related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

**(3) Status of Claims**

The statement of the status of the claims contained in the brief is correct. The following is a list of claims that are rejected and pending in the application:

Claims 1-6, 8, 22 and 24-40 are pending and rejected.

**(4) Status of Amendments After Final**

An after-final amendment was submitted on June 4, 2010. By that amendment, claims 1 and 6 were amended. The advisory action of July 8, 2010 indicates that the proposed amendment will be entered, and that claims 1-6, 8, 22 and 24-40 remain rejected.

**(5) Summary of Claimed Subject Matter**

The examiner has no comment on the summary of claimed subject matter contained in the brief.

**(6) Grounds of Rejection to be Reviewed on Appeal**

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

**(7) Claims Appendix**

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

**(8) Evidence Relied Upon**

WO 00/11208

AEBERSOLD ET AL.

2-2000

Moutiez, E, Prognon, P., Bourrinet, P., Zehaf, S., Dencausse, A. and Mahuzier, G.  
“Time-resolved Luminescence as a Novel Detection Mode for the Simultaneous High-performance Liquid Chromatographic Determination of Gadolinium-DOTA and  $Gd^{3+}$ ”,  
Analyst, Vol. 122, (1997), pages 1347-1352

Li, H., Siu, M., Guevremont, R. and Blanc, J. " Complexes of Silver(I) with Peptides and Proteins as Produced in Electrospray Mass Spectrometry", J. Am Soc, Mass Spectrm, Vol. 8, (1997) pages 781-792.

**(9) Grounds of Rejection**

The following ground(s) of rejection are applicable to the appealed claims:

**Claim Rejections - 35 USC § 103**

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-6, 8, 22, 24-38 and 39-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aegersold et al. (WO 00/11208, from IDS) in view of Moutiez et al (Analyst 1997, 122, pp 1347-1352) and Li et al. (J. Am. Soc. Mass spectro. 1997, 8, pp 781-792).

Aebersold et al. teach a method of identification and quantification of a protein in a sample by cleaving the protein to peptides using a proteolytic enzyme (page 18, paragh. 4) and using a reagent A-L-PRG, wherein A is linked to a solid support (wherein, A comprises biotin, oligohistidine, etc, page 12) and is covalently linked to linker L (L contain metal bound chelate, page 14, 2<sup>nd</sup> paragh. and may contain disulfide group, which is cleavable, page 6, last paragh.); PRG comprises a sulfhydryl group, or an enzyme substrate (page 6, 2<sup>nd</sup> paragh.) N-hydroxysuccinimide ester groups, etc (claim 32 of Aebersold et al.) to bind to the cleaved peptides. Aebersold et al. teach the use of a tandem technique comprising electrospray ionization mass spectrometry coupled with liquid chromatography (HPLC/ESI-MS/MS (FIG 7), peptide sequence information (page 19, 2nd paragh.) combined with isotope tags for qualitative and quantitative analysis of the protein in a sample. Although Aebersold et al. teach the use of a linker L being labeled with isotopes, they do not label the proteins with said isotope. The A-L-PRG reagent of Aebersold et al (similar to appellants' A-Y-PRG) comprises a chelated metal ion and the stable isotope in their L and use the stable isotope as standard in mass spectrometric analysis. However Aebersold et al. do not use a reagent A-Y-PRG wherein said reagent is not isotopically labeled and does not use metal ion as a standard in mass spectrometric analysis.

Use of metal ion as a standard in mass spectrometric studies is well known in the prior art (see page 781, Li et al.). Li et al. teach a well characterized spectra of peptide bound silver ion in mass spectral analysis (Figure 1, page 783.)

It is well known in the art the advantage of purifying and detecting proteins using chelated metal tags comprising various metal ions (Porath et al Prot express and Pur. 1992, 3, 263-281, from IDS) using a variety of chelating agents, such as lanthanide metal ions with

DOTA (Moutiez et al). Moutiez et al teach a  $Gd^{3+}$  ion chelated to DOTA and teach its separation using metal ion chelate affinity chromatography (page 1350 2<sup>nd</sup> column) and teach that lanthanide metal complex can be detected using luminescence technique (page 1347 2<sup>nd</sup> column 2<sup>nd</sup> paragraph).

Therefore in order to identify and quantify proteins in proteomic samples, one of ordinary skill in the art is **motivated** to modify the A-L-PRG of Aebersold et al with  $Gd^{3+}$  DOTA chelate not being modified by isotope label and use the metal ion as standard (as taught by Li et al) in the method of Aebersold et al, because a peptide sample attached to L-PRG with  $Gd^{3+}$  DOTA can be separated by metal ion chelate affinity column by HPLC, and optionally can be detected by luminescence before passing into the mass spectrometer.

As such, it would have been obvious to one of ordinary skill in the art to combine the teachings of Aebersold et al, Moutiez et al and Li et al to make an A-L-PRG reagent having  $Gd^{3+}$  DOTA complex in L, use it in the method of identification and quantification of proteins in a sample by a tandem technique comprising electrospray ionization mass spectrometry coupled with liquid chromatography (HPLC/ESI-MS/MS (FIG 7), peptide sequence information using Gd metal ion as standard, and optionally detecting the  $Gd^{3+}$  DOTA attached polypeptide by using luminescence before passing the sample into the Mass spectrometer.

#### **(10) Response to Argument**

On pages 5-12 of the Brief, Appellants argue that claims 1-6, 8, 22, and 24-40 are patentable because the claimed invention is not obvious over Aebersold et al. (WO 00/11208, from IDS) in view of Moutiez et al (Analyst 1997, 122, pp 1347-1352) and Li et al. (J. Am. Soc. Mass spectro. 1997, 8, pp 781-792). Appellants argue that the Examiner has not shown a prima

facie case of obviousness because (1) The rejection fails to establish a prima facie case of obviousness for the claimed invention , and (2) The cited combination of references fails to teach all the limitations of the claimed invention, (3) The modification of Aebersold et al., as proposed in the office action would render the teach unsuitable for their intended purpose. (4) the obviousness rejection of the record is an improper hindsight reconstruction of the claimed invention. The Examiner will address arguments presented by Appellant in the Brief.

**1. The rejection fails to establish a prima facie case of obviousness for the claimed invention.**

On pages 6- 7 of the Brief, Appellant argues that the examiner has not established prima facie case obviousness for the claimed invention because examiner just combined the teaching of Aebersold et al. (WO 00/11208, from IDS) in view of Moutiez et al (Analyst 1997, 122, pp 1347-1352) and Li et al. (J. Am. Soc. Mass spectro. 1997, 8, pp 781-792) and provide nothing more than conclusory statements as to the obviousness of the claimed invention. Appellants' argument is considered but found unpersuasive. Appellants argue that one skilled in the art would not modify the reagent A-L-PRG of Aebersold et al. having isotope label in L with a chelated metal ion in L and use metal ion as a detecting ion in mass spectrometry. Appellants further argue that the rejection fail to articulate any rationale for replacing isotopic labels from the reagent A-L-PRG and replace it with chelated metal ion. Appellants' arguments are considered but found unpersuasive. It is well known in the art that in mass spectrometric technique isotope label (Aebersold et al.) and metal ion label (Li et al) are use to detect analyte in the detector. There are advantages to use chelated metal ion as label compare to isotope label, such as the advantage of purifying and detecting proteins using chelated metal tags



comprising various metal ions (Porath et al Prot express and Pur. 1992, 3, 263-281, from IDS) using a variety of chelating agents, such as lanthanide metal ions with DOTA (Moutiez et al). Therefore, one of ordinary skill in the art is motivated to replace isotope label of the reagent A-L-PRG of Aebersold et al. with A-L-PRG having chelated metal ion because sample can be separated by metal ion chelate affinity column by HPLC and furthermore, in the case of  $Gd^{3+}$  DOTA as a chelated metal ion, optionally can be detected by luminescence before passing into the mass spectrometer. Accordingly a prima facie case of obviousness has been established.

**2. The cited combination of references fails to teach all the limitations of the claimed invention.**

Appellants' argue at page 8 that none of the three references teach or suggest a method of identification and quantification of a protein in a sample utilizing a reagent A-Y-PRG and using a tandem technique comprising electrospray ionization mass spectrometry coupled with liquid chromatography (HPLC/ESI-MS/MS and peptide sequence information combined with metal tags for qualitative and quantitative analysis of the protein in a sample. Appellants' arguments have been fully considered, but they found unpersuasive. Aebersold et al teach a method of identification and quantification of a protein in a sample utilizing a reagent A-L-PRG and using a tandem technique comprising electrospray ionization mass spectrometry coupled with liquid chromatography (HPLC/ESI-MS/MS and peptide sequence information combined with isotope tags for qualitative and quantitative analysis of the protein in a sample. Therefore appellants method uses the reagent A-Y-PRG having metal chelate in Y ; and Aebersold et al method uses A-L-PRG having isotope in L and the two methods are identical except prior method use metal ion as detection ion in mass spectrometry and later method use isotopic ion mass spectrometry. If

Aebersold et al were to teach a metal labeled reagent and use chelated metal ion as detection ion in the MS detector, they would anticipate appellants' invention. However as explained above other references teach the advantages of using metal ion labeled reagent. As explained above, Li et al. teach a well characterized spectra of peptide bound silver ion in mass spectral analysis. It is well known in the art the advantage of purifying and detecting proteins using chelated metal tags comprising various metal ions using a variety of chelating agents. Therefore in order to identify and quantify proteins in proteomic samples, one of ordinary skill in the art is **motivated** to modify the A-L-PRG of Aebersold et al with chelated metal ion, such as  $Gd^{3+}$  DOTA chelate not being modified by isotope label and use the metal ion as standard (as taught by Li et al) in the method of Aebersold et al, because a peptide sample attached to L-PRG with  $Gd^{3+}$  DOTA can be separated by metal ion chelate affinity column by HPLC, and optionally can be detected by luminescence before passing into the mass spectrometer.

**3. the modification of Aebersold et al., as proposed in the office action would render the teachings unsuitable for their intended purpose.**

Appellants at pages 9-10 argue that modification of Aebersold et al teaching (i.e. modifying A-L-PRG, having isotope label in L of Aebersold et al by A-L-PRG having metal ion in L) render the prior art invention being modified unsatisfactory. Appellants' argument is considered but found unpersuasive. Appellants argue that Aebersold et al use the isotope label reagent to detect peptide sample using ICAT methodology (detect isotopic ion as a detection ion) in mass spectrometric detection. Appellants argue that ICAT method of detection is different than appellants' method of detection of metal ion (Appellants defined as MeCAT). Appellants further argue that elimination of isotopically labeled reagent from L of A-L-PRG would have

eliminated one's ability to detect sample (in this case peptide) on the basis of mass. Appellants' argument is considered but found unpersuasive. Only difference in the two methods is the "detection ion" in Mass spectrometric detection. Therefore only difference between method of detection of protein sample using A-L-PRG reagent of Aebersold et al and a method of detection protein sample using A-L-PRG having chelated metal ion L is mode of detection of MS signal in the detector. Aebersold et al use ICAT (detection of isotopic ion) and later method use metal ion detection in the detector. Both method of detection of ions in Mass spectrometric detection is well known in art (isotope label (Aebersold et al.) and metal ion label (Li et al)). Appellants further argue that elimination of isotopically labeled reagent from L of A-L-PRG would have eliminated one's ability to detect sample (in this case peptide) on the basis of mass. Appellants' argument is considered but found unpersuasive. Both reagents, A-L-PRG having isotopically labeled reagent of Aebersold et al. and the reagent having metal chelate in A-L-PRG are identical except detecting ion in mass spectrometric detector. It is well known in the art that in Mass spectrometry isotope label (Aebersold et al.) and metal ion label (Li et al) are use to detect analyte in the detector. There are advantages to use chelated metal ion as label compare to isotope label such as it is also well known in the art that chelated metal ion is used widely in HPLC separation of analyte (Moutiez et al). One of ordinary skill in the art is motivated to replace isotope label of the reagent A-L-PRG of Aebersold et al. with A-L-PRG having chelated metal ion because can be separated by metal ion chelate affinity column by HPLC and further in the case of  $Gd^{3+}$  DOTA as a chelated metal ion optionally can be detected by luminescence before passing into the mass spectrometer.

**4) The obviousness rejection of the record is a improper hindsight reconstruction of the claimed invention.**

On pages 11-12 of the brief appellants argue that an improper hindsight reconstruction of the claimed invention. Appellants' argument is considered but found unpersuasive. Appellants argue that Aebersold et al. reagent A-L-PRG comprises isotopically labeled L and replacing isotopically labeled L in A-L-PRG by metal chelated L would have rendered the teaching of Aebersold et al. unsuitable for the intended purpose. Appellants argue that one of skill in the art would not be motivated to modify Aebersold et al. reagent A-L-PRG comprising isotopically labeled L and replacing isotopically labeled L in A-L-PRG by metal chelated L to detect protein using method of Aebersold et al ( method of identification and quantification of a protein in a sample using a tandem technique comprising electrospray ionization mass spectrometry coupled with liquid chromatography (HPLC/ESI-MS/MS and peptide sequence information combined with metal tags for qualitative and quantitative analysis of the protein in a sample) . Appellants' argument is considered but found unpersuasive. Both reagents, A-L-PRG having isotopically labeled reagent of Aebersold et al. and the reagent having metal chelate in A-L-PRG are identical except detecting ion in mass spectrometric detector. It is well known in the art that in Mass spectrometry isotope label (Aebersold et al.) and metal ion label (Li et al) are use to detect analyte in the detector. There are advantages to use chelated metal ion as label compare to isotope label such as the advantage of purifying and detecting proteins using chelated metal tags comprising various metal ions (Porath et al Prot express and Pur. 1992, 3, 263-281, from IDS) using a variety of chelating agents, such as lanthanide metal ions with DOTA (Moutiez et al). One of ordinary skill in the art is motivated to replace isotope label of

the reagent A-L-PRG of Aebersold et al. with A-L-PRG having chelated metal ion because can be separated by metal ion chelate affinity column by HPLC and further in the case of  $Gd^{3+}$  DOTA as a chelated metal ion optionally can be detected by luminescence before passing into the mass spectrometer.

The Examiner has provided the rationale to support a conclusion that the claims would have been obvious in that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art; KSR, 550 U.S.398,419 (2006); Sakraida v. AG Pro, Inc., 425 U.S. 273, 282, 189 USPQ 449, 453 (1976); Anderson 's-Black Rock, Inc. v. Pavement Salvage Co., 396 U.S. 57, 62-63, 163 USPQ 673, 675 (1969); Great Atlantic & P. Tea Co. v. Supermarket Equipment Corp., 340 U.S. 147, 152, 87 USPQ 303, 306 (1950).

For the above reasons, it is believed that the rejections should be sustained.  
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